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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PHILADELPHIA, PA 19103-2307

EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,068	LEVY ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-66* is/are pending in the application.

4a) Of the above claim(s) *36-39,47-50 and 61-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,35,40-46,51-60,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040920*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 35, 40, 46, 51, 60, and 65, directed to the agent being denatured collagen in the reply filed on 3/8/06 is acknowledged. The traversal is on the ground(s) that the various linked inventions are not independent, i.e. they are not unconnected in "design, operation, or effect", and there would be no serious burden to search and examine all of the groups. This is not found persuasive because they are distinct, for the reasons of record. While the various inventions are connected in ultimate effect, i.e. increase cytoskeletal permissiveness so as to increase transfection efficiency (at least in theory), they are not connected in design and/or operation. The various compounds used in the different methods are structurally and functionally different compounds that have different direct effects and lead to the ultimate effect by different means at the molecular level. With respect to a serious burden for search and examination, Applicant merely asserts that there is no burden because of their hypothetical functional relationship in increasing cytoskeletal permissiveness. However, a search of all the various inventions cannot be based on Applicant's hypothesis alone or the terms used by Applicant to describe that hypothesis. A complete search of the invention would require a search of every agent disclosed. Since these compounds are structurally and functionally different, they clearly would have to be searched separately. i.e. art on one would be unlikely to disclose another. Such separate, non-overlapping searches constitutes a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 36-39, 47-50, and 61-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/8/06.

Applicant asserts (Election, page 5) that claims 34, 45, and 59 have not been accounted for. In response, these claims and claims 41-44, 52-58 and 66 were identified as generic linking claims on page 6 of the restriction requirement. As such, they are not placed in any group directed to a single invention. Claims 34, 41-45, 52-59, and 66 have been examined only to the extent required to determine that they are not allowable. That they have not been found to be allowable is further evidence that the restriction requirement is proper.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/851,327, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claim 53 is directed to a composition for enhancing efficiency of delivery of a nucleic acid to a "vascular smooth muscle cell." The only place in the '327 specification mentioning "vascular smooth muscle cells" (page 24, lines 1-4) is a discussion of the function of tenascin C produced in vascular smooth muscle cells, and does not describe using an "agent" to enhance transfection of vascular smooth muscle cells. Examples 1-3 describe transfecting A10 cells, an immortalized cell line derived from rat arterial smooth muscle cells, but does not teach that vascular smooth muscle cells in general are intended targets of the method.

Claim 56 is directed to a composition for enhancing efficiency of delivery of a nucleic acid "comprising a carrier that permits controlled release" of the agent. Page 16, lines 12-13, of the '327 specification describe combining the agent with "a *polymeric* carrier *such as a controlled release film or nanoparticle or microparticle*" (emphasis added). It does not describe some generic carrier, which would include non-polymeric carriers or carriers in a form other than a film, nanoparticle or microparticle, to which claim 56 is now directed. Claim 57 specifies that the composition comprising the carrier is coated onto a tissue or organ localizing device, and claim 58 specifies that the device is a stent or vascular or urinary catheter. Page 18, lines 13-17, describe delivery of agent or nucleic acid delivery system to the cell by techniques that include "using tissue or organ localizing devices, such as wound dressings or transdermal delivery systems, using invasive devices such as vascular or urinary catheters, and using interventional devices such as stents having drug delivery capability and configured as expansive devices or

stent grafts". It does not describe coating such devices with a composition comprising a carrier that permits controlled release, and it does not generically describe catheters or stents as tissue or organ localizing device, but rather as invasive devices and interventional devices, respectively.

Thus, the '327 application fails to support the embodiments of the invention of claims 53 and 56-58, and the effective filing date for this subject matter is the instant filing date of 9/5/03.

In addition, a reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. The instant application was filed as a division of the '327 application. For the reasons set forth above, the subject matter of instant original claims 53 and 56-58 are not supported in the '327 application. Consequently, the instant application is a continuation-in-part of the '327 application, not a division.

To rectify this discrepancy, Applicant is required to either a) amend the first sentence of the specification, which was inserted in the preliminary amendment filed 9/5/03, to indicate the instant application is continuation-in-part of the '327 application; or b) cancel claims 53 and 56-58, in which case the application would properly be a division of the '327 application. Failure to take appropriate action in the reply to the instant Office action to rectify this discrepancy will be considered to be non-responsive to this Office action. Whichever option is chosen, it must be consistent with the option chosen to address the objection to the specification set forth below.

In addition, the reference to the '327 application must be updated to include that the application issued as U.S. Pat. No. 6,919,208.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

The instant application was filed with a preliminary amendment, but without an executed oath or declaration. The later filed declaration fails to properly identify the application as having been amended on 9/5/03 (see line 8 of the declaration filed 5/13/04). Applicant is required to provide a substitute declaration that identifies the amended application to which it applies by indicating the date the amendment was filed. Also see 37 CFR 1.63 (b)(2).

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required. The specification does not describe using the claimed composition to transfect a "vascular smooth muscle cell" (claim 53), a generic "carrier that permits controlled release ..." (claim 56), coating a "tissue or organ localizing device" with a composition comprising the agent and nucleic acid (claim 57), or a "tissue or organ localizing device" as

including a "stent", "vascular catheter" or "urinary catheter" (claim 58). This may be corrected either a) by amending the specification to provide proper antecedent basis for the claimed subject matter, or b) by canceling claims 53 and 56-58. Whichever remedy is chosen, it must be consistent with the remedy chosen to correct the relationship between this application and the '327 application as set forth above.

Claim Objections

Claims 34, 35, 41-46, 52-60, and 66 are objected to because of the following informalities: these claims embrace non-elected inventions. Appropriate correction is required prior to allowance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 35, and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing transfection of cultured cells with cationic liposomes comprising plasmid by growth in the presence of tenascin C or denatured collagen before, during, or after transfection or cytochalasin D after transfection, does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The compositions of these claims include limitations taught in the specification only as being for *in vivo* use.

The claims are directed to a method for enhancing transfection of a cell either *in vitro* or *in vivo* by providing an "agent capable of enhancing the cytoskeletal permissiveness of said cell for transfection." Based on three working examples performed with a cultured arterial smooth muscle cell line, Applicant speculates that the enhanced transfection was due to "increasing the cytoskeletal permissiveness for transfection." Growth of the cells on denatured collagen (gelatin) or with tenascin C before and after transfection, or in the presence of cytochalasin D after transfection with cationic liposomes comprising plasmid DNA was observed to have an enhancing effect on transfection. No working examples with other agents are provided, nor of transfection *in vivo.* The guidance provided by the specification is minimal with respect to selection of agents that could be expected to increase "the cytoskeletal permissiveness for transfection," or how such agents would be provided to cells, particularly *in vivo.*

The only criterion disclosed for identifying "enhanced cytoskeletal permissiveness" *a priori* is whether the actin depolymerization results. Denatured collagen and tenascin C induce expression of TB4 in the smooth muscle cells. TB4 is an actin binding protein which sequesters G-actin, and thus driving actin polymerization/depolymerization in the favor of depolymerization. Applicant has proposed that any agent which leads to the depolymerization of actin in general should enhance transfection. Cytochalasins bind the end of an actin fiber to

prevent further polymerization, which may lead to fragmentation of actin filaments. (It is not known to cause depolymerization *per se* as suggested in the specification.) No experimental results are described which confirm that the transfection results observed were in fact due to the effect of the agents on cytoskeletal changes. For example, determining whether tenascin C or denatured collagen required an active TB4 gene in the target cell in order to enhance transfection. Matrigel is known to induce expression of TB4 (Grant et al., J. Cell Sci. 108 (Pt. 12): 3685-3694, Dec. 1995). However, growing cells on Matrigel before or during transfection leads to a decrease in transfection efficiency (Shih et al., Biotechniques 18 (5): 813, 814, 816, May 1995; and Pasco et al., DNA 8 (7): 535-541, Sep. 1989), which contradicts the speculation that induction of TB4 would improve transfection. Also, exposure of cells to a cytochalasin prior to transfection with cationic liposomes is known to inhibit transfection (Watanabe et al., J. Biochem. 116 (6): 1220-1226, Dec. 1994), which contradicts the speculation that blocking actin polymerization (at least before transfection) would enhance transfection.

With respect to the agent being TB4 itself, There is no guidance as to how TB4 would be effectively delivered to the cell. Unlike denatured collagen and tenascin C, which act at the cell surface, TB4 is a cytosolic protein. Unlike cytochalasins, proteins are not freely diffusible across a cell membrane. While methods are known for introducing proteins into cells, these methods are not used in conjunction with transfection, and there is no evidence of record that such methods could deliver TB4 in a manner that would allow enhancement of transfection, as opposed to inhibiting transfection. Consequently, it is left entirely to one of skill in the art to develop a method to effectively deliver TB4 to cells in conjunction with transfection such that transfection would be enhanced.

With respect to transfection *in vivo*, the claims require that transfection with the agent be enhanced over absence of the agent. As indicated above, there are no relevant working examples of *in vivo* transfection. Nor is there any guidance as to how the agent should be administered to cells *in vivo* in a manner such that transfection is enhanced relative to the absence of the agent. Orkin et al. reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The specification (page 1) acknowledges, citing Orkin, that effective delivery of genes *in vivo* was hampered by a "dearth of effective gene transfer vectors." As indicated in Orkin, pages 8-10, transfection with naked DNA or DNA-liposomes is substantially lower in efficiency than are viral vectors; and the efficiency with viral vectors, generally, is not high enough. The instant invention is aimed at overcoming this particular problem. However, there is no evidence of record that the claimed invention would improve transfection efficiency *in vivo* at all, much less improve it enough to overcome this problem.

Therefore, in view of state of the art, the high unpredictability of *in vivo* transfection, the lack of relevant working examples for *in vivo* transfection, the lack of guidance commensurate in scope with the claims, and the amount and nature of the experimentation required to develop those embodiments of the invention for which guidance and examples are lacking, it would require undue experimentation to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 65 recites the limitation "[T]he method of claim 60" in line 1. There is insufficient antecedent basis for this limitation in the claim, as claim 60 is directed to a "kit" not a "method". For the purpose of compact prosecution, it is assumed that the claim is directed to the "kit" of claim 60.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

As noted above, claim 65 is indefinite in its recitation of the "method of claim 60." but has been interpreted to be directed to the kit of claim 60 for the following.

Claims 34, 35, 40-46, 51, 53, 55, 59, 60, 65, and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Arrow et al., US 5,849,902.

Arrow (col. 6-7) describes a method of transfecting HeLa cells with a plasmid encoding a heterologous protein or polypeptide comprising culturing the cells on a plate coated with denatured collagen (gelatin) then exposing the cells to a liposomal preparation comprising Lipofectin™, which is a vehicle suitable for pharmaceutical delivery, comprising the plasmid. This is basically the same general method as described in instant example 1. The final

transfection mixture is a composition comprising the denatured collagen and the nucleic acid. Given that the cell is in contact with the gelatin coating before, during, and after exposure to the nucleic acid, the method meets the limitations of claims 41-43. Claim 53 recites an intended use that does not materially affect the composition. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal permissiveness. Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method.

Claims 34, 35, 40, 41, 44-46, 51-60, 65, and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isner, US 5,652,225.

Isner discloses a method for gene therapy comprising delivery of a vector comprising a nucleic acid encoding a heterologous polypeptide or protein to arterial endothelium and smooth muscle using a vascular balloon catheter coated with a hydrogel, such as denatured collagen (gelatin), containing the vector. The vector may be naked plasmid DNA, an adenovirus or cationic liposome. See entire document, especially, col. 1-3, 4-9, claims 1-6. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re*

Gulack, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal permissiveness. Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method.

Claims 34, 35, 40, 41, 44-46, 51-54, 56, 59, 60, 65, and 66 are rejected under 35 U.S.C. 102(a) & (e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Truong et al., US 6,025,337.

Truong describes a composition of microparticles comprising denatured collagen (gelatin) and a plasmid vector comprising nucleic acid encoding a heterologous protein or polypeptide, and a method of using same to transfect mammalian cells *in vitro* and *in vivo*. Such microparticles are characterized by controlled release of their constituents. See entire reference, for example col. 2 and claims 1-16 and 27-37. With respect to claim 53, the limitation that the cell is a vascular smooth muscle cell limits the intended use of the claimed composition, and does not materially distinguish the claimed composition from that described by Truong. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal permissiveness.

Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633